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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,554	01/14/2004	Christine Lindsay Mummery	17360	5975

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EXAMINER	
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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,554	MUMMERY, CHRISTINE LINDSAY	
	Examiner	Art Unit	
	MAGDALENE SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45,46,50-54,60,61,63-65,68-71,87-89,91 and 133* is/are pending in the application.

4a) Of the above claim(s) *63 and 91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,46,50-54,60,61,64,65,68-71,87-89 and 133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/01/2011 has been entered.

Claims 45-46, 50-54, 60-61, 63-65, 68-71, 87-89, 91, 133 are pending. The amendment has been entered. Claims 63, 91 are withdrawn. Claims 1-44, 47-49, 55-59, 62, 66-67, 72-86, 90, 92-132 are canceled.

Claims 45-46, 50-54, 60-61, 64-65, 68-71, 87-89, 133 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. The rejection of claim **60** for the phrase "substantially" is withdrawn in view of the amendment of the claim dated 03/01/2011.

B. Claims **46, 50-54, 60-61, 64-65, 68-71, 87-89, 133** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims **51, 133 stand** rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons of record dated 10/01/2010.

Applicants argue the specification clearly describes criteria to identify what are visceral endoderm-like properties so as to identify visceral endoderm-like cells. As stated on page 10

and 11, visceral endoderm may be identified by expression of alpha-feto protein (AFP) and cytokeratin (ENDO-A). Hence, "VE-like cells", as used in the present application, can be identified by the marker expression of endoderm proteins. The embryonic cell, which is used to co-culture hES cells in the claimed methods, may be derived from an embryonic cell line, preferably a cell line with characteristics of visceral endoderm (see page 14, line 29). The cell line having characteristics of visceral endoderm is a visceral endoderm-like cell. Applicant's arguments have been fully considered but are not persuasive.

In response the term "-like" includes elements not actually disclosed such as the disclosed AFP and ENDO-A markers, thereby rendering the scope of the claim unascertainable The specification also teaches human embryonic stem (hES) in co-culture with END-2 cells after a period of 13 days the differentiated stem cells have mixed morphology but with a relatively high proportion of epithelial-like cells [0033]. Therefore, it is uncertain if "like" confers markers for endothelial- or epithelial cell markers.

Applicants argue Examiner's attention is directed to the fact that the visceral endoderm of the embryo is not generally thought to contribute to adult somatic tissue but to extra-embryonic tissue lineages. The Examiner is confusing visceral endoderm with the definitive endoderm of the embryo that is formed later in embryonic development during gastrulation and does contribute to the formation of the somatic lineages that the Examiner has indicated. The marker expression profile defined in the specification provides evidence that the END2 mouse cell type has the visceral endoderm-like character, i.e., it exhibits a protein expressing profile of embryonic visceral endoderm. Accordingly, the specification provides a clear description for identifying visceral endoderm-like cells, which a person skilled in the art can rely on to identify the cells. Furthermore, Applicant submits that the use of this terminology is not uncommon for describing cells in developmental biology. In fact, the USPTO has granted claims to other "cell-

like" types. For example, "mesenchymal and fibroblast-like" cells that have been described in U.S. Patent No. 6,642, 048, and are recited in the claims of the '048 patent. For instance claim 23 of US 6,642,048 reads: 23. The composition of claim 18, wherein the cells used to condition the medium have been obtained by differentiating a culture of hES cells, and then selecting mesenchymal or fibroblast- like cells from the culture. Applicant's arguments have been fully considered but are not persuasive.

In response, each office action stands on its own merits. In the instant case, the term "-like" enters the derivation of the embryonic stem cell unascertainable because it embraces embryonic cells derived from adult visceral endoderm tissue or adult endoderm-like tissue which may not express AFP or ENDO-A marker as embryonic cells derived from extra-embryonic tissue lineages. The phrase "visceral endoderm-like" can mean digestive system cell or tissue, gland cell or tissue, part of respiratory cell or tissue, or no visceral endoderm-like at all. It is unclear what kind of "visceral endoderm-like" or to what extent is intended for the phrase "visceral endoderm-like". It is also unclear what kind of "visceral endoderm-like" cell expresses alpha-feto protein. Thus, the rejection is maintained.

Claim **69** recites the limitation "the stem cells" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. There is no species of stem cells, wherein the limitation is referred to. This is because claim 45 relates to a single stem cell, an HES cell. There are not plural cells, and thus there is lack of antecedent basis.

Claims **46, 50-54, 60-61, 64-65, 68-71, 87-89, 133** are dependent from claim 45

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 45-46, 50-54, 60-61, 64-65, 68-71, 87-89 under 35 U.S.C. 103(a) as being unpatentable over Amit et al (Developmental Biology, 227: 271-278, 2000) in view of Mummery et al (Differentiation, 46: 51-60, 1991); Rohwedel et al (Cells Tissues Organs, 165:190-202, 1999 (Abstract)); Rohwedel et al (Dev Biol, 164(1): 87-101, 1994 (IDS)) is withdrawn.

Claims 45-46, 50-54, 60, 64-65, 68-71, 87-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Amit et al** (Developmental Biology, 227: 271-278, 2000) in view of **Mummery et al** (Differentiation, 46: 51-60, 1991); **Eiges et al** (Current Biology 2001, 11:514–518, 2001); **Klug et al** (J Clin Invest, 98(1): 216-224, 1996 (IDS)).

Amit et al teach co culture of human embryonic stem cells (hES) plated on irradiated mouse embryonic fibroblasts (MEFs) (p 272, under materials and methods). Amit teaches the fibroblast feeder layer remains the most poorly defined component of the human ES cell culture environment (p 276, 2nd column last paragraph bridge to p 277) **(claims 45-46, 64-65, 68, 71, 87-89).** Amit suggests however, fibroblasts can produce LIF, and given the importance of LIF in the culture of human embryonic germ (EG) cells further examination of the role of LIF in human ES cell self-renewal is warranted. Identifying the factors that the fibroblasts produce that promote human ES cell renewal will be critical to the large-scale growth of ES cells, because the feeder layers are labor intensive to prepare and because variation between batches of fibroblasts can introduce undesirable variation and complexity to experiments (p277). Amit teaches that serum is a complex mixture that can contain compounds both beneficial and detrimental to human ES cell culture (p 276, 1st column). Different serum batches vary widely in

their ability to support vigorous undifferentiated proliferation of human ES cells (p 276). Replacing serum with defined components should reduce the variability of experiments associated with serum batch variation and should allow more carefully defined differentiation studies (p 276). Amit suggests the need for substantial improvements to the serum-free culture of human ES cells (p 276) as well as the fibroblast feeder layer remains the most poorly defined component of the human ES cell culture environment. Amit suggests most important, the present culture conditions support a cloning efficiency of human ES cells (<1%) that is considerably lower than the cloning efficiency of mouse ES cells in order to apply signaling to mouse ES cells technology, such as homologous recombination, will be very difficult to apply to human ES cells (p 276). Amit differs from the present invention for not teaching the co-culture of END-2 cells with human embryonic stem cells (hES).

However, at the time of the instant invention **Mummery et al** (1991) showed that P19 embryonal carcinoma (EC) cells differentiate into beating heart muscle cells at high rates in the presence of co-cultures of END-2 cells (visceral endoderm-like cell lines) (abstract, and p 53, 1st column under cell culture). Mummery (1991) also teaches the co-cultures in which the feeder cells and the P19 EC cells were cultured in the presence of charcoal stripped serum for depletion of retinoic acid (see p 53, 1t column, under cell culture). In addition, Mummery (1991) teaches the co-cultures in which the feeder cells and the P19 EC cells were separated were prepared by plating layer of 1% agar over confluent feeder and as such meets the limitation of a cellular matrix (see p 53, 1st column, under cell culture) **(claims 60-61).** Mummery (1991) teaches the END-2 feeder cells expressed alpha feto protein thus indicative of the END-2 cell is derived from visceral endoderm(p 53, 2nd column) **(claims 50-54).** Mummery (1991) also teaches conditioned medium from END-2, had a similar effect, suggesting that visceral-endoderm-like cells secrete a factor capable of inducing a differentiation program in a

pluripotent EC cell line.(p 53, 1st column, 1st paragraph). Mummery teaches the P19 EC cells became exquisitely sensitive to the inducing action of RA, forming beating muscle at 10^{-9} M (Fig. 5 b) or even 10^{-10} M (p 58, 1st column, last paragraph).

Eiges et al (Current Biology 2001, 11:514–518, 2001) teaches introducing the EGFP reporter gene under the control of a promoter of an ES cell-enriched gene into human ES cells (p 514, 2nd column, 1st paragraph). Eiges teaches tagging the undifferentiated cells with GFP, to monitor the differentiation status of the cells in culture during growth and propagation as well as following spontaneous and induced differentiation (p 514, 2nd column, 1st paragraph) **(claim 70).** Eiges teaches transfection using the promoter sequence of the murine *Rex1* gene and by introducing *Rex1*-regulated gene markers (*Rex1*-EGFP) into human ES cells, allowing the determination of the differentiation status of these cells in culture (p 514, 2nd column, 1st paragraph). Eiges report the first isolation of genetically engineered human ES cell lines and describe an efficient protocol for transfecting these cells (p 517, 2d column, 4th paragraph). Eiges teaches by introducing genetic modifications into their genome, should be able to manipulate them in vitro and use them as vectors in cell-based therapies as well as for other biomedical and research purposes (p 517, 2d column, 4th paragraph).

Klug et al (J Clin Invest, 98(1): 216-224, 1996 (IDS)) teaches genetic manipulation can be used to select essentially pure cultures of cardiomyocytes from differentiating mouse ES cells and to date, ES lines capable of cardiogenic differentiation have been generated in a number of species, including mouse, and if cardiomyocyte engraftment proves to be of therapeutic value, and suggests the generation of hES cells (p 223, 1st column, last paragraph). Klug suggests the existence of pluripotent human embryonic carcinoma cell lines is encouraging with regards to the prospects of generating cardiogenic human ES cells (p 223, 1st column, last paragraph). As such, Klug provides a nexus for generating cardiogenic hES cells and of

pluripotent human embryonic carcinoma cell lines in the context of genetic manipulation used to select essentially pure cultures of cardiomyocytes from differentiating mouse ES cells.

Accordingly, it would have been obvious to culture the hES cells of Amit in a system taught by Mummery to produce differentiated mesoderm cells or cardiomyocytes or vascular endothelial cells with a reasonable expectation of success. Further it would have been obvious to genetically modify the hES cells by introducing *Rex1*-regulated gene markers (*Rex1*-EGFP) into human ES cells, allowing the determination of the differentiation status of the cells in culture such as taught by Eiges taken with Klug, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to make this modification in order to induce cellular differentiation of hES cells in view of the teachings of Klug who provides a nexus for generating cardiogenic hES cells and of pluripotent human embryonic carcinoma cell lines in the context of genetic manipulation used to select essentially pure cultures of cardiomyocytes from differentiating mouse ES cells. This is further underscored by the teachings of Mummery that P19 embryonal carcinoma (EC) cells differentiate into beating heart muscle cells at high rates in the presence of co-cultures of END-2 cells (visceral endoderm-like cell lines) (abstract, and p 53, 1st column under cell culture). As such it would have been obvious to use mouse EC protocol with human ES cells in view of the combined teachings of Amit using human ES cells for differentiation under co-culture with feeder cell conditions combined with the teachings of Mummery using mouse EC cells for co-culture with END-2 cells resulting in differentiation into beating heart muscle cells at high rates in the presence of co-cultures of END-2 cells (visceral endoderm-like cell lines).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Applicant's amendments to the claims and arguments are persuasive for the rejection mailed 03/01/2011. However, the arguments are not rebutted as they are not relevant to the new rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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